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REVIEW —*Current Perspective*—

Neurobiology of the Edg2 Lysophosphatidic Acid Receptor

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ABSTRACT—Lysophosphatidic acid (LPA, 1-acyl-*sn*-glycerol-3-phosphate) is a well-known lipid growth factor that is found widely in various tissues including brain and is reported to drive different intracellular signaling pathways. In the nervous system, LPA studies have drawn many neuroscientists' attention because it has some actions related to neurogenesis such as cell rounding and proliferation. Remarkable advances in this field have been obtained along with the discovery of the cDNA clone for its receptor, vzg1/edg2, a member of the seven transmembrane-type edg family. Successive studies have revealed that edg2 activation by LPA mediates several neurobiological actions related to neurogenesis, neuronal excitability and survival activity on developing and postnatal neurons. Here we focused their molecular basis of signaling through G proteins and in vivo roles of edg2 in such neurobiological events.

Keywords: Neurogenesis, Edg, Rho, Lysophosphatidic acid

1. G-protein-mediated actions of LPA and related lysophospholipid

Lysophosphatidic acid (LPA) as well as sphingosine-1-phosphate (S1P) are representative lipid growth factors, and they are biosynthesized de novo mainly through a stimulus-coupled liberation of glycerophospholipids and sphingolipids and subsequent enzymatic conversions (1).

LPA causes various cellular events, including proliferation, changes of cell shapes, motility, membrane excitability and neurotransmitter release (2 – 10). All these actions are reported to be mostly mediated through various kinds of G proteins (G_i, $G_{12/13}$, $G_{q/11}$). In addition to the involvement of several different G proteins in LPA actions, the discovery of different types of LPA receptors and the presence of S1P, a similar phospholipid, make the understanding of molecular mechanisms of LPA actions more difficult.

2. Discovery of edg family phospholipid receptors and their signaling through G proteins

The discovery of the first LPA receptor, vzg1 has contributed to molecular basis of understanding of biological activities of lysophospholipids. Vzg1 has been cloned from the ventricular zone of embryonic cerebral cortex (11). This receptor is highly expressed throughout the neurogenetic period. The receptor increased responsiveness to LPA in cell rounding and adenylyl-cyclase inhibition assays when overexpressed in cortical cell lines. The vzg-1 receptor is a member of endothelial cell differentiation gene (edg) family of G-protein-coupled receptors (GPCRs). By homology screening and other approaches totally eight different cDNAs of edg have been discovered (12). The edg family of orphan receptors comprises edg1, edg2/Rec1.3/vzg-1, edg3, edg4, edg5/AGR16/H218, edg6, edg7 and edg8. This family contains LPA receptor and another receptor for S1P that is a lipid mediator structurally related to LPA. According to amino acid sequence homology, ligand specificity and genomic structure, these GPCRs of the edg family are classified into the LP_A-group including edg2, edg4 and edg7 for LPA and LP_B-group including edg1, edg3 and edg5 for S1P (Table 1). Edg6 and edg8 have been recently cloned and characterized as receptors for S1P (13 – 15). The cannnabinoid CB_1 receptor is the non-edg GPCR, though it shares some amino acid homology to the edg receptors. The CB_1 receptor has <30% amino acid homology with any edg protein (16). Two endogenous lipids, anandamide and 2-arachidonylglycerol, may be the ligands for this drug receptor (17, 18). Moreover, a novel GPCR, named PSP24, which does not show significant sequence homology with any member of the edg family, has also been isolated from *Xenopus* oocytes as a functional receptor for LPA (19).

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Table 1. LPA and S1P receptors in the edg family

Receptor number	Ligand	LP designation	Alternative name	Possible coupled G proteins	Tissue distribution
edg2	LPA	LP_{A1}	vzg-1, rec1.3	G_i, G_o, G_{11}, G_{12}, G_{13}	ubiquitous highest abundance in brain
edg4	LPA	LP_{A2}	—	G_i, G_q	leukocyte, thymus, spleen, testis, prostate, pancreas
edg7	LPA	LP_{A3}	—	G_q	heart, pancreas, prostate, testis, lung, ovary
edg1	S1P	LP_{B1}		G_i	ubiquitous
edg3	S1P	LP_{B2}		G_i, G_q, G_{13}	cardiovascular, leukocyte
edg5	S1P	LP_{B3}	AGR16, H218	G_i, G_q, G_{13}	cardiovascular, central nervous system, gonadal tissues, placenta
edg6	S1P, SPC	—	—	G_i	lymphoid and hematopoietic tissue, lung
edg8	S1P	—	nrg-1	G_i	spleen, brain

SPC: sphingosylphosphorylcholine.

Among LP_A-group, the edg2 transcripts were found in almost all human tissues with the highest abundance in the brain (20). In contrast, the edg4 and edg7 transcripts were not found in human tissues as widely as edg2 transcripts and they were almost not detectable in the brain (20, 21) (Table 1). Therefore various neuronal effects by LPA may be mostly mediated through edg2 receptor, although it remains to be determined whether a wide variety of LPA-actions through various G proteins is simply attributed to the actions through edg2. However, recent studies revealed that edg2 could functionally activate G_i, G_o and G_{11}, G_{12} and G_{13}. Accordingly, the possibility that edg2 mediates multiple brain functions can not be excluded.

3. Neurogenesis and LPA receptor

As vzg-1, mouse edg2 homologue, is expressed within the embryonic ventricular zone, edg2 is speculated to be both temporally and spatially related to the period of cortical neurogenesis. During early development, cortical cerebral neurons are generated from a discrete proliferative region overlying the cerebral ventricles, the ventricular zone (22). Cortical neuroblasts display a stereotyped change in their morphology that is linked to their proliferation (Fig. 1). During the S-phase of the cell cycle, ventricular zone neuroblasts appear bipolar, with the cell body at the superficial margin of the ventricular zone and with processes oriented towards the ventricular and superficial surfaces of the cerebral wall. With the progression of cell cycle, neuroblasts undergo "interkinetic nuclear migration". During the G2 phase, nucleus descends to the ventricular surface, processes are retracted and finally the cell "round up" (16). After rounding, the cell undergoes mitosis and then regains its bipolar morphology to complete the cell cycle (Fig. 1). There is a possibility that the edg2 receptor might mediate these neurogenic events, since LPA possesses such morphological and proliferative actions in some cell lines and primary culture neurons.

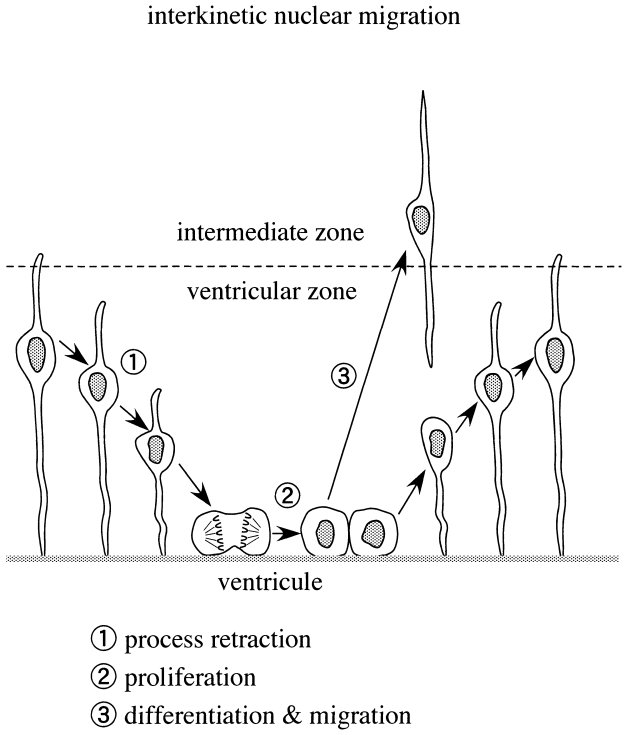

Fig. 1. Interkinetic nuclear migration of neuroblasts in ventricular zone during embryonic neurogenesis.

Rho-mediated signaling in morphological change: LPA stimulates morphological changes via activation of a Rho-dependent pathway that is blocked by botulinum neurotoxin C3 (BoTxC3) (Fig. 2A). In various cells, Rho is activated through G_{12} and G_{13}, which are activated by some receptors, including receptors for thrombin,

thromboxane A_2 and LPA (23 – 25). LPA activates both G_{12} and G_{13}, but this activation of G_{12} was apparently not linked to stress fiber formation (23). On the other hand, there is a report that LPA-induced stress fiber formation is mediated through $G\alpha_{13}$ and epidermal growth factor (EGF) receptor (26) (Fig. 2A). In that report, an inhibitor for EGF receptor-specific tyrosine kinase or the expression of dominant negative mutant of EGF receptor prevented the LPA-induced stress fiber formation via G_{13} activation (Fig. 2A).

Neuronal cells also undergo rapid growth cone collapse, neurite retraction and cell rounding in response to LPA (8, 27). The LPA-induced neurite retraction could not be prevented by palytoxin (PTX)-treatment or expression of dominant negative Ras (8), suggesting that PTX-sensitive G proteins and their downstream mechanisms through the mitogen-activated protein (MAP) kinase pathway are unlikely involved. In N1E-115 neuronal cells, on the other hand, the microinjection of Rho-inactivating BoTxC3 promoted formation of filopodia and lamellipodia, and prevents actomyosin-based neurite retraction and cell rounding induced by LPA (28). In addition, LPA activates Rho kinase to induce growth cone collapse and neurite retraction through a G_{13}-mediated pathway that involves protein-tyrosine kinase activity (29) (Fig. 2A). Recently, the downstream events of Rho kinase involved in the neurite retraction have been reported (30, 31). A tyrosine phosphorylation of focal adhesion kinase (FAK) was enhanced during neurite retraction by LPA, which was reduced by BoTxC3 or Rho kinase inhibitor (30). Another report showed that the Rho kinase phosphorylated collapsin-response-mediator protein-2 (CRMP-2) in chick dorsal root ganglion neurons during LPA-induced growth cone collapse (31). In addition, the overexpression of a negative mutant CRMP-2 inhibited LPA-induced growth cone collapse. These data suggest that LPA-induced Rho kinase activation is involved in neurite retraction through CRMP-2 phosphorylation (Fig. 2A).

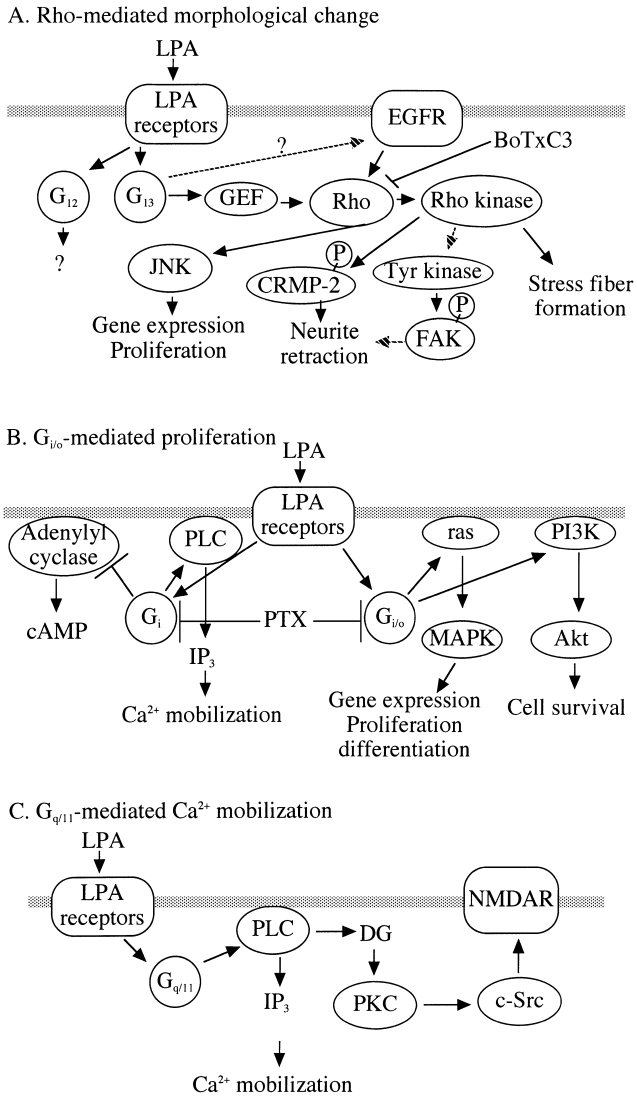

Fig. 2. LPA-induced cellular action and its intracellular signal transduction pathways. A: Rho-mediated morphological changes, B: $G_{i/o}$-mediated proliferation, C: $G_{q/11}$-mediated Ca^{2+} mobilization.

Recently it was reported that RhoGEF, a putative GDP /GTP exchange factor, might transduce the G_{13}-signal to Rho. The expression of recombinant RhoGEF induced cell rounding and neurite outgrowth (32), while $G\alpha_{13}$ directly regulates RhoGEF through a RGS (regulators of G protein signaling)-like domain (33) (Fig. 2A). It is interesting to note that RGSs regulate the LPA signaling through trimeric G protein activation.

Signaling of LPA-induced proliferation: It is well known that the activation of the G_i-Ras-MAP kinase pathway mediates transcriptional activation of immediate-early genes, subsequent DNA synthesis and cell proliferation (34 – 37). This mechanism is also reported to be involved in LPA-induced cell-proliferation (10). Recent studies demonstrated that LPA-induced activation of MAP kinases (Erk1 and Erk2) through G_i signaling is negatively regulated by some RGSs (38). Recently, a Grb2-associated binder-1 (Gab1) is reported to be involved in Erk2 activation by LPA through edg2 (39), although the involvement of G_i remains unclear.

Several studies demonstrated that edg2 functionally couples to G_i. This fact indicates that LPA-mediated activation of edg2 may contribute to the proliferation in neurogenesis (Fig. 2B). We reported that edg2 functionally couples to G_{i1} as well as G_{oA} and G_{11}, but not G_s in reconstitution experiments measuring [^{35}S]GTPγS binding in the baculovirus expression system (40). From the Scatchard Plot analysis, we found that edg2 has basal activity to stimulate G_{i1}, but not G_{oA} without stimulation by LPA. It is interesting to note that the high level expression of edg2

specific for the early stage of neural development may itself stimulate neural proliferation.

On the other hand, LPA-induced cell proliferation through $G\alpha_{12}$ and $G\alpha_{13}$ has been also reported. In this mechanism, Rho activation is involved in Jun NH_2-terminal kinase/stress-activated protein kinase (JNK) pathway (41, 42) (Fig. 2A).

Other mechanisms in neurogenesis: Although it is evident that LPA may be involved in the morphological changes and mitogenesis in neurogenesis, it has been unclear whether LPA directly stimulates the neuroblast during neurogenesis. A recent report showed that neuroblasts can respond to LPA application with multiple ionic conductance changes (43). The whole-cell patch clamp technique revealed that some cortical cells at embryonic day 11 responded only to LPA but not to GABA or L-glutamate. These LPA-responsible cells were then found to be nestin-positive and to incorporate BrdU.

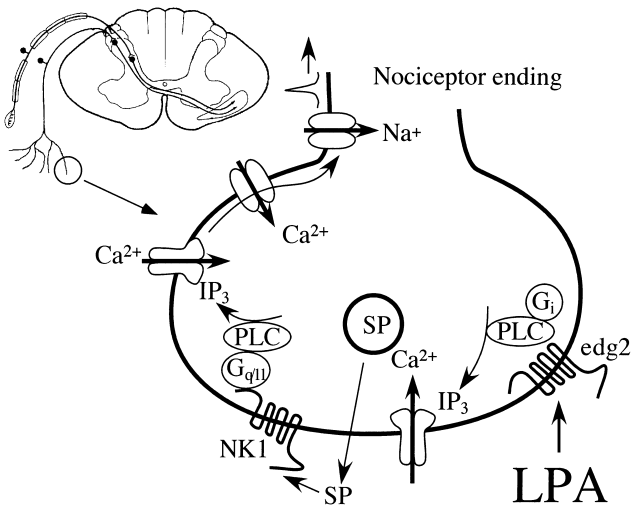

Fig. 3. Molecular mechanisms of LPA-induced nociception at peripheral nerve ending. NK1: neurokinin 1 receptor.

4. Roles of edg2 in various functions in postnatal nervous system

Although the gene expression of edg2 in the postnatal nervous system is quite low, compared to the case with developing brain, there are some intriguing reports that LPA affects mature neurons. LPA can regulate NMDA-receptor function indirectly through a G-protein-coupled receptor activation and PKC-dependent activation of the non-receptor tyrosine kinase (Src) signaling cascade (44) (Fig. 2C). LPA caused growth cone collapse in chick dorsal root ganglion neurons, retinal neurons, and sympathetic ganglion cells as well as neuronal cell lines (45). Moreover, LPA-treatment of rat hippocampal neurons resulted in necrosis and apoptosis at high and low concentration, respectively (46).

LPA receptor edg2 is expressed in oligodendrocytes and Schwann cells (SCs) during development (47), suggesting an influence of LPA on the myelinating cells. LPA shows a potent survival activity for cultured neonatal SCs (48). Pharmacological studies revealed that the survival activity by LPA is mediated by G_i, phospholipase C (PLC) and Akt pathway (Fig. 2B). Overexpression of edg2 decreased SC apoptosis even in the absence of LPA, although it is unclear whether endogenous LPA is involved there.

Recently, we found nociceptive actions of LPA in the peripheral flexor test in adult mice (49). These actions were proved to be mediated through an action on nociceptor endings of primary afferent neurons, by the experiment using antisence oligodeoxynucleotide. In addition to it, the activation of PTX-sensitive G proteins and substance P (SP) release from nociceptor endings were found to be involved in the in vivo signaling of LPA-nociception (Fig. 3). Series of our extensive studies strongly suggested that G_i-coupled receptor-induced nociception is attributed to the SP release from nociceptor endings of polymodal C-fiber by activation of inositol 1,4,5-trisphosphate (IP_3)-induced Ca^{2+} mobilization (50).

5. Perspective

Accumulating evidence suggesting that edg2 LPA receptor expressed in the early stage of neuronal development may play an important role in embryonic neurogenesis. In adult brain, on the other hand, the receptor becomes more expressed in glia cells. Through a regulation of proliferation and differentiation of neurons and glia cells, the edg2 LPA receptor may be involved in the neuronal network maintenance. To study whether this receptor is involved in the adult brain neurogenesis would be also an interesting subject. Further studies using conditional knock-out mice would provide the answer to this question.

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